

REMARKS

Upon entry of this Amendment, Claims 1-10 and 12-18 are pending in the application. Claims 6-8 and 13 are withdrawn. Claims 15-18 are new and have support throughout the specification, for example on page 2, lines 12-14, page 4, lines 30-33 spanning into page 5, lines 1-3 and page 7, lines 16-18. No new matter has been introduced into the application by way of the present claim amendments. Minor amendments have been made to the claims to simply overcome the rejections under 35 U.S.C. § 112 and to clarify the claimed subject matter. The Examiner is respectfully requested to reconsider and withdraw the rejection(s) in view of the amendments and remarks contained herein.

ELECTION/RESTRICTION

Applicant has withdrawn Claims 6-8 and 13 which are drawn to non-elected claims. Applicant reserves the right to file additional divisional applications for the prosecution of the invention defined by the non-elected claims during the pendency of this application.

INFORMATION DISCLOSURE STATEMENT

Applicant is concurrently filing a Supplemental Information Disclosure Statement and Form 1449 attached with the missing references WO99/50391, Macias et al., Nindl et al., and Spadara as requested by the Examiner. (Office Action at page 3). Accordingly, Applicant requests that these missing references be considered by the Examiner

REJECTION UNDER 35 U.S.C. § 112

Claims 1-5, 9-12, and 14 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner has alleged that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

As amended herein, Claim 1 is drawn to a method of treating a tissue defect in a human or other animal subject, comprising the steps of: (a) culturing a living tissue in a medium to form a tissue culture; (b) subjecting said tissue culture to an electromagnetic field for at least 8 hours; (c) extracting said medium from said tissue culture; and (d) administering said medium to the site of said tissue defect, wherein said medium is capable of inducing proliferation or regeneration of at least one cell type which provides a therapeutic effect in or near said tissue defect. Claim 1 is drawn to the regeneration or proliferation of one or more cell types in or near the tissue defect that upon forming a critical number of cells, the cell type(s) are capable of correcting the tissue defect or provide a therapeutic effect to a tissue defect, for example the proliferation of endothelial cells which then go on to form blood vessels in or near tissue defects such as hypoxic muscle tissue, or for example, at or near bone fractures, orthopedic implant sites or in acute or chronic wounds. (See specification at page 4, lines 1-10, and Examples 1 & 2). Other therapeutic effects are also contemplated to overcome other types of tissue defects, for example, formation of new bone in bone defects by inducing regeneration and/or proliferation of bone cells in the bone defect. The bone cells synthesize and/or replace osseous tissue in bone defects. (See specification, for example at page 8, lines 30-32 and page 9, lines 1-7).

The Office Action alleges that the complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. (Office Action at page 4). Applicant respectfully submits that the specification teaches various examples that are representative of the breadth of the claimed subject matter. The specification amply demonstrates to one of ordinary skill in the art how to make and use the claimed compositions and their use in the claimed methods to treat tissue defects of any kind. Specific defects taught in the specification and throughout the examples include: vascular defects, bone defects, skin defects and organ tissue defects. Each of these various defects are treatable using the methods described in the instant specification. Methods of making the claimed compositions are amply described to allow one of ordinary skill in the art to make and use the compositions without undue burden. For example, the selection of the living tissue to be cultured can be tissue defect specific or tissue defect non-specific. The specification teaches, for example on page 5, lines 31-32 and page 6, lines 1-4 that the living tissue cells to be cultured can include stromal cells. These cells can be tissue specific, i.e. cells taken from or near the tissue defect, for example as part of a biopsy that can have a direct therapeutic effect to the defect where they were isolated.

Alternatively, the living tissue can comprise cells that are non-specific to the tissue defect. Several of the stromal cells taught in the specification, for example, endothelial and/or fibroblast cells derived from adult or fetal tissue have the capability of providing several growth factors and other biological active molecules known to those of skill in the art at the time of filing this application, that confer bioactivity to a wide range of different cell types implicated in many different types of tissue defects. In some cases the living tissue can be readily obtained from the subject, or they may be allogenic or xenogenic.

Applicant respectfully submits, that the application as filed supports the breadth of tissue defects that can be treated based on the description of living tissues that can be employed to yield conditioned media capable of providing regenerative and proliferation signaling to at least one cell type at or near the tissue defect. Applicant submits that there are sufficient working examples that would enable one of ordinary skill in the art to: (a) select the appropriate cell type (cell-line, tissue biopsy or tissue from an autopsy) to culture (i.e. a cell type that can provide a proliferation and/or regeneration signal that is effective in growing at least one cell type that can provide a therapeutic effect to the tissue defect, for example, endothelial cells that can form tubules that ultimately form blood vessels near the tissue defect (angiogenesis), (b) expose the cultured cells using an electromagnetic source, for example, Helmholtz coils and equivalent sources of electromagnetic fields known in the art, (c) extract the medium used to grow the living tissue using various commonly known liquid evacuation techniques, and (d) administering the medium to the defect site, either through administration of the medium directly, (liquid, or lyophilisate) or in admixture with a pharmaceutically-acceptable carrier, for example, a gel, a scaffold, osteoconductive matrix and the like.

Such teachings are amply illustrated throughout the specification and in particular, Examples 1-3 provided on pages 9-11.

The Office Action further alleges that there is a lack of working examples to “demonstrate the effectiveness of the instant invention in treating any tissue defect.” (Office Action at page 4). The Applicant respectfully disagrees. Angiogenesis was adequately demonstrated using the methods described in exemplified embodiments of Example 3 on page 11, lines 5-26. Example 3 demonstrates that the conditioned media obtained after incubation of the media with HUVEC cells was effective in inducing a proliferative response in human

umbilical vein endothelial cells which is known to serve as a model for angiogenesis therapy. As stated in the MPEP § 2164.02, “A single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled...The presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors.” Applicant respectfully submits, that the other factors discussed below tends to show, that on the balance of the evidence, the specification as filed enables of ordinary skill in the art to make and use the claimed invention as of the date of filing.

Moreover, the Office Action alleges that a large quantity of experimentation would be required to identify all tissue cultures exposed to an electromagnetic field which result in media which are effective in treating all tissue defects. (Office Action at page 4). The Applicant submits that when the Wands Factors are examined, a reasonable conclusion can be formed that provides that the specification’s guidance and level of ordinary skill in art are sufficient to enable the claimed invention to be practiced without undue experimentation.

The Applicant submits that the exemplified embodiments requires a living tissue to be cultured in tissue culture medium and that the medium be administered to the tissue defect. As adequately and amply described in the specification, the living tissue can be selected from any tissue, illustrative examples can include: vascular, skin, skeletal and organ tissues. (Specification at page 5, lines 1-3) Moreover, additional examples of tissue samples for culturing can include useful cells that are capable of inducing regeneration and proliferation of at least one cell type at or near the tissue defect, for example, tissues from autologous, allogenic and xenogenic sources. These tissues can comprise stromal cells as disclosed in the specification at page 5, lines 14-23. It appears that the Examiner is placing an unnecessary restriction that each and every tissue

defect must be treated with a unique living tissue culture: “Finally, one would need to perform a large quantity of experimentation to identify all tissue cultures exposed to electromagnetic field which result in media which are effective in treating all tissue defects, of which there are many types with complex and different characteristics’ (Office Action at page 4, lines 13-16). Applicant respectfully submits, that there may be a great many tissue defects that can be treated with a known cell culture or living tissue which provides regenerative or proliferative signals to many different types of cells that can be therapeutic for many different tissue defects. The living tissue, for example, may produce pleiotrophic factors that can stimulate the differentiation and growth of more than one cell type in one or several different tissue defects.

The state of the prior art and the level of one of ordinary skill is sufficiently high to enable one of ordinary skill in the art, guided by the specification, to practice the methods and prepare and use the compositions described in the exemplified embodiments. One of ordinary skill in the art at the time of filing could have tested one or more living tissues, using no more than routine tissue culture methods to evaluate whether the resultant conditioned media can produce a regenerative and/or proliferative effect on at least one cell type at or near a tissue defect that could lead to a therapeutic effect. Although in some instances, several routine tests may be required to determine whether one or more culture media is/are capable of inducing regeneration and/or proliferation of at least one cell type capable of producing a therapeutic effect, the specification provides adequate guidance to make this testing merely routine.

Moreover, the relative skill in the art is high. A technician experienced in tissue culture and medical experimentation could readily evaluate whether an administered medium to a tissue defect has resulted in a therapeutic effect. The therapeutic effect could easily be determined by an analysis of the degree of vascularization present in the defect (specification at page 5, lines

30-33, and page 4, lines 1-5 and Example 2) the growth and fracture strength of bone tissue in the defect (Example 2), and the extent and rapidity of wound healing (specification, Example 1) are illustrated as a number of examples.

Applicant has also added new Claims 15-18 which recite the treatment of bone defects and wound healing defects. Applicant submits that these two defects are further specifically enabled by the specification as filed, for example on page 4, lines 7-11, lines 15-23, lines 30-32 and page 5, lines 1-3. Examples 1-3 are, in particular, specifically describe methods of treating wound and bone defects.

Applicant respectfully submits that the specification as filed, provides adequate guidance to one of ordinary skill in the art how to make and use the compositions of the present invention without undue experimentation. Accordingly, Applicant respectfully requests that the present rejection be reconsidered and withdrawn.

Claims 2 and 3 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

Applicant has amended Claims 2 and 3 to provide antecedent basis to the terms: “living tissue” and “electromagnetic field” as suggested by the Examiner thus obviating the present rejections under 35 U.S.C. § 112, second paragraph.

Applicant respectfully requests that the present rejection be reconsidered and withdrawn accordingly.

REJECTION UNDER 35 U.S.C. § 102

Claims 9, 11, and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Baylink (U.S. Pat. No. 5,195,940 issued March 23, 1993) herein after “*Baylink*”. This rejection is respectfully traversed.

At the outset, Applicant respectfully submits that *Baylink* fails to anticipate the amended Claim 9 drawn to compositions for the treatment of tissue defects in a human or other animal subject, comprising a safe and effective amount of a medium produced by electromagnetic stimulation of a tissue culture for at least 8 hours and a pharmaceutically-acceptable carrier.

In contrast, *Baylink* fails to teach or disclose a composition that can be used to treat tissue defects comprising a medium produced by pulsed electromagnetic field radiation for at least 8 hours and a pharmaceutically-acceptable carrier. *Baylink* discloses that a specific objective of the invention is to provide non-invasive techniques for stimulating the production of growth factors in the tissue of interest. (*Baylink* at Col. 1, lines 7-13.) The production of the growth factor occurs within the living tissue (or in vivo) (*Baylink* at Col. 2, lines 5-8). *Baylink* fails to disclose a composition comprising a medium produced by electromagnetic field of a tissue culture for at least 8 hours and a pharmaceutically-acceptable carrier.

The Applicant respectfully disagrees with the Office Action’s characterization, that a “pharmaceutically-acceptable carrier” can also be a tissue culture medium. Otherwise, *Baylink* merely describes human osteocarcinoma cells grown in a pharmaceutically acceptable carrier and not a medium. Applicant respectfully asserts, that the Examiner has the burden of establishing with some evidence, that a tissue culture medium is considered by one of ordinary skill in the art to be a “pharmaceutically-acceptable carrier” as construed in the Applicant’s exemplified embodiments. The Applicant has illustrated representative examples of

pharmaceutically-acceptable carriers as including: saline, hyaluronic acid, cellulose ethers (such as carboxymethyl cellulose), collagen, gelatin, an osteoconductive carrier, and mixtures thereof.

Applicant respectfully submits that *Baylink* fails to teach, suggest or disclose a composition comprising a safe and effective amount of a medium produced by electromagnetic stimulation of a tissue culture for at least 8 hours and a pharmaceutically-acceptable carrier as recited in Claim 9. Claim 11 has been cancelled herein. Claim 14 is also patentable by virtue of its dependence on Claim 9.

Accordingly, Applicant respectfully requests that the present rejection under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

Claims 9, 11, and 14 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by George et al. (U.S. Pat. No. 6,334,069, issued December 25, 2001) herein after “*George*”. This rejection is respectfully traversed.

George is drawn to a method and an apparatus for the treatment of chronic wounds using pulsed electromagnetic energy. In Example 1, the fibroblasts plated in “96-well trays at initial densities from 500-10,000 cells per well in Dulbecco’s modified Eagle’s medium supplemented with high (10% horse, 5% fetal calf) or low (0,5% fetal calf) serum.” [Emphasis added]. In Example 2 the cells were pulsed for 0-60 min.

Applicant submits that *George* also fails to disclose, teach or suggest compositions comprising a pharmaceutically-acceptable carrier as illustrated in the Applicant’s exemplified embodiments. For the same reasons articulated above in *Baylink*, Applicant respectfully disagrees with the Office Action’s contention that the tissue culture medium (Dulbecco’s modified Eagle’s medium commonly referred to as DMEM in the presence of high or low horse/fetal calf serum) is a pharmaceutically-acceptable carrier. Applicant respectfully submits

that DMEM containing high concentrations of horse and fetal calf serum as disclosed in *George* at Col. 18, lines 34-37 would not be considered as pharmaceutically-acceptable, particularly to those with IgE type allergies to equine and bovine products. Moreover, fetal calf serum may provide the more dangerous causative agent(s) of bovine spongiform encephalopathy (BSE). Thus, neither *George* (nor even *Baylink*) teaches or suggests the use of a composition comprising a tissue culture medium in a pharmaceutically acceptable carrier for implantation into a defect.

Moreover, *George* fails to disclose a medium in which the cell culture was pulsed with electromagnetic radiation for a period greater than at least 8 hours. Support for this claim amendment can be found in the specification as originally filed at page 7, lines 16-18.

REJECTION UNDER 35 U.S.C. § 103

Claims 1-5, 9-12, and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Naughton et al. (U.S. Pat. No. 6,372,494, issued April 16, 2002) herein after referred to as “*Naughton*” in view of *Baylink* and/or *George*. This rejection is respectfully traversed.

Naughton is drawn to compositions comprising conditioned media and three dimensional tissue constructs for various therapeutic purposes, including wound healing, and to repair and correct a variety of anomalies, both congenital and acquired as well as cosmetic defects, both superficial and invasive. (Naughton at Col. 25, lines 39-41). Applicant notes, however, that *Naughton* fails to provide even one working example showing that any defect or even the presence of growth factors isolated from the conditioned media are capable of enhancing the proliferation of any cell type useful in any stated therapeutic application.

In particular, *Naughton* provides a conditioned media that contains various growth factors and other therapeutic products produced by human cells that have been cultured for period of

time to produce a desired level of extracellular products. *Naughton* preferentially describes three-dimensional cell constructs versus two-dimensional cell constructs: “The cell type, whether cultures in two-dimensions or three-dimensions, will affect the properties of the conditioned medium. A three-dimensional construct is preferred.” (*Naughton* at Col. 10, lines 12-15). As one of ordinary skill would expect, a three-dimensional construct can take days to weeks to become established and longer for the use of the three-dimensional construct as a scaffold for other cells as disclosed in *Naughton* (See, Col. 14, lines 49-55). In fact, *Naughton* is silent as to how long a cell culture of any lineage is required to be incubated in a medium to produce any therapeutic agent to any desired concentration. One of ordinary skill in the art simply does not know for how long to incubate the cells to obtain a composition that is therapeutic for any of the conditions and disorders recited in *Naughton*. The Applicant’s method overcomes this length of time delay problem associated with *Naughton*, by providing a method to treat a tissue defect utilizing electromagnetic field exposure of cell cultures, to produce a medium that is effective in cell-growth and regeneration in 24 hours or less. *Naughton* fails to disclose or even suggest the desirability of irradiating the cell cultures with such an electromagnetic field.

Baylink and *George*, on the other hand, both disclose in vivo administration of electromagnetic field radiation to effect the proliferation and regeneration of at least one cell type that is capable of providing a therapeutic effect in a tissue defect. Such administration is in vivo, however, not in vitro. *Baylink* expressly states: “Thus, the tissue region of living tissue which is to be stimulated , is a region of living tissue **in a subject** or, in other words, **in vivo target tissue**. (emphasis added, *Baylink*, Col. 5, lines 32-35). Moreover, *George* states: “More particularly, it is an object of this invention to provide an electromagnetic energy treatment apparatus with the ability to produce a constant, known and replicable treatment dosage output

that is not adversely affected (i.e., does not negate consistent dosage of efficacy) **by the proximity of the body of the patient** (e.g. capacitance, inductance.” (emphasis added, *George*, at Col. 6, lines 20-26). In short, both *Baylink* and *George* disclose and teach apparatus to be applied on the body or in vivo of the human subject in a non-invasive manner to effect increased growth and proliferation of cells **in vivo**.

Thus, contrary to the Examiner’s contention, one of ordinary skill in the art would not have implemented the electromagnetic fields used in *Baylink* and *George* on a tissue culture to produce a therapeutic effect in a patient, because patient tissue defects in *Baylink* and *George* were only deemed treatable by exposing the patient with the electromagnetic field in vivo, and not by administration of a medium that is exposed in vitro to electromagnetic fields. In fact, *Baylink* and *George* teach away from administering anything to the patient other than the non-invasive pulsed magnetic field to treat the defect. For to do so, would vitiate any advantage gained by developing an apparatus that delivers pulsed electromagnetic fields to the living tissue of the patient/subject.

Finally, it should be noted that *Baylink* and *George* exposed their samples with doses of radiation lasting less than 60 minutes. One of ordinary skill in the art would not have a reasonable expectation of success in treating a defect using the method of *Naughton* modified by *Baylink* and/or *George*, because the desired levels of growth factors produced in *Naughton* (days to weeks of incubation) would not be achievable after exposure of the same cell cultures for periods of 60 minutes or less as disclosed by *Baylink* and *George*.

Claim 11 has been cancelled herein and this rejection is rendered moot with respect to Claim 11.

Accordingly, Applicant submits that *Naughton*, *Baylink*, or *George* either individually, or in combination, fail to render Claims 1 and 9 and dependent Claims 2-5, 10, 12 and 14 obvious. Applicant respectfully requests that the present rejection of Claims 1-5 and 9-10, 12 and 14 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Claims 1, 3, 9, 11, 12, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shipley et al. (WO 93/04164) in view of *Baylink* and/or *George*.

Shipley is directed to the production of growth factors by human epithelial cells (keratinocyte-derived conditioned medium factors (kdCMF) in protein free medium and using the same to increase the rate of wound healing. Claim 11 has been cancelled, rendering moot the rejection of that claim.

Applicant submits that the same difficulties and inconsistencies outlined above in practicing the combined methods of *Naughton* and those of *Baylink* and *George* using the compositions obtained thereby are similarly found in *Shipley*. Namely, there is no objective suggestion or motivation to combine a slow process of growth factor production in *Shipley* (see Example 1 in *Shipley*: “After 1-3 days of incubation, the cells are washed 3 times...After 24 hours of additional incubation...Protein-free standard medium conditioned by human keratinocytes is collected every 24-48 hours for 4-5 days...”) with the relatively rapid in-vivo treatment of *Baylink* and *George*. There is simply no reasonable expectation of success to combine a method that takes at least 6 or more days to produce sufficient growth factor for treatment as taught in *Shipley* and expect that the same quantity of growth factors required for treatment can be produced in 60 minutes or less using cell-cultures exposed to electromagnetic fields produced using the apparatus described by *Baylink* and/or *George* for in-vivo use. One of ordinary skill in the art would not be motivated to combine the two methods and derive the methods and compositions as disclosed and taught by the Applicant.


Accordingly, Applicant submits that *Shipley*, *Baylink*, or *George* either individually, or in combination, fail to render Claims 1, 3, 9, 11, 12, and 14 obvious. Applicant respectfully requests that the present rejection of Claims 1, 3, 9, 12, and 14 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

CONCLUSION

Applicant respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

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